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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/509,668	01/04/2005	Jacopo Zanon	407-US-PCT	9567
45821	7590	07/31/2008		
LUNDBECK RESEARCH USA, INC. ATTENTION: STEPHEN G. KALINCHAK, LEGAL 215 COLLEGE ROAD PARAMUS, NJ 07652			EXAMINER O'DELL, DAVID K	
			ART UNIT	PAPER NUMBER
			1625	
			MAIL DATE	DELIVERY MODE
			07/31/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/509,668

Applicant(s)

ZANON ET AL.

Examiner

David K. O'Dell

Art Unit

1625

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 27 March 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-20 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-20 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SF/ICE)
- 4) ☐ Interview Summary (PTO-413)
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____
- Paper No(s)/Mail Date _____

DETAILED ACTION

1. Claims 1-20 are pending in the current application.
2. This application is a 371 of PCT/DK03/00208 filed 03/26/2003 which claims benefit of U.S. Provisional 60/368,434 filed 03/27/2002, and Danish application, PA 2002 00480 filed 03/27/2002.

Response to Arguments

3. Applicants' representative's arguments filed on March 27, 2008 have been fully considered but they are not persuasive. The rejections of the claims under 35 U.S.C. 112 2nd is maintained, but restated since the claims have been amended in a manner insufficient to overcome the rejection. With respect to the rejection under 35 U.S.C. 103 (a) for obviousness, the rejection of the claims is maintained for the reasons of record. Applicants' representative has argued (remarks at 8), that there is no motivation to use the Method A of Perregaard to produce 5-cholro-1-(4-fluorophenyl)-indole and that Perregaard teaches away from using the method A to prepare 5-cholro-1-(4-fluorophenyl)-indole. With respect to the argument that there can be found no motivation to use method A in the teaching of Perregaard, the examiner disagrees since Perregaard et. al. states that "The Ullmann arylation procedure (method A, Scheme 11) was preferred". Moreover, it should be made clear that while the broad claims read on the actual conditions of Perregaard, the narrower claims are drawn to the improved conditions of both Klapars and Kang (where the Ullmann arylation is performed with diamine ligands). It is clear that in the instant case the motivation to use this method not only resides in the teaching of Perregaard, but also in the improved, milder conditions of the Ullmann arylation developed by Klapars and Kang. One cannot show nonobviousness by attacking references individually where

the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In addition the applicants' representative has argued that Perregaard et. al. teaches away from method A by pointing to the fact that Perregaard et. al. stated that "certain indoles are inaccessible or at least inconveniently prepared by methods A or B in large scale quantities" and that method C was actually used to make 5-cholro-1-(4-fluorophenyl)-indole. To take a closer look at the remarks of Perregaard with respect to method A is warranted:

"The Ullmann arylation procedure (method A, Scheme 11) was preferred when 1-unsubstituted indoles (7) were either commercially available at reasonable costs and quantities or if they could be conveniently prepared according to known methods."

So with respect to method A, it seems clear that cost or ease of preparation of the starting materials was the primary factor and that this is the reason that "certain indoles are inaccessible or at least inconveniently prepared by methods A or B in large scale quantities". This makes it very clear that it was not a question of the effectiveness of method A, but rather in the context of a large scale synthesis the cost of the starting materials was a serious concern. It is known that the starting 5-cholro-indole is difficult to prepare on a large scale see U.S. 4,377,699 discussion columns 1 & 2 and the improvement described therein utilizes, rather inconveniently, chlorine gas in the chlorination step. Moreover the instant disclosure does not recite any new synthesis of 5-cholro-indole and as such is limited in the same way as the prior art. This argument might be valid if the instant claims provided a remedy for the high cost of 5-cholro-indole by providing a new synthesis, but of course this is not the case.

Another argument presented to the examiner is that based upon the teaching of the prior art, that it would be unlikely for an electron deficient indole like 5-cholro-indole of the instant

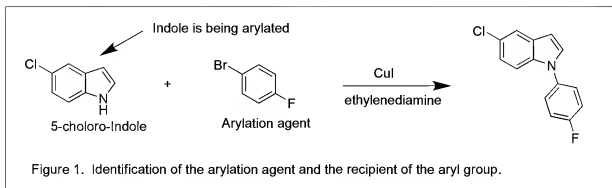
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case to undergo the Ullmann arylation. This is not persuasive because Perregaard et. al. clearly show that indoles that are unarguably much more electron deficient than 5-chloro-indole readily undergo the Ullmann arylation (method A) including 5-fluoroindole, (see Table II entries 10b, 10c, 10d reproduced below):

Table II. 1-(4-Fluorophenyl)-1H-indoles (10)

compd	X	method ^a	mp, °C	formula ^b
10a	H	A	40	C ₁₆ H ₁₂ FN
10b	NO ₂ ←	A	144-146	C ₁₆ H ₉ FN ₂ O ₂
10c	CN ←	A	110-112	C ₁₆ H ₉ FN ₃
10d	F ←	A or B	oil ^c	
10e	CH ₃	B	oil ^c	
10f	CF ₃	C	53	C ₁₉ H ₁₀ F ₃ N
10g	CH ₃ SO ₂	C	126	C ₁₉ H ₁₀ FNO ₂ S
10h	Cl	C or D	88-87	C ₁₆ H ₉ ClFN
10i	OCH ₃	D	96	C ₁₇ H ₁₃ FNO
10j	Br	D	101	C ₁₇ H ₁₀ BrFN

The remainder of the argument on pages 11 to 14 seem to be grounded in a lack of understanding as to what the arylation agent actually is. The applicants' representative has misidentified the arylation agent as 5-chloroindole, however the arylation agent is a phenyliodide or phenylbromide, not the 5-chloroindole, which is being arylated, as in Example 32, shown below in Figure 1.



Addressing subsequent arguments founded on this misinterpretation is not possible.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

The facts of this case are very clear, and may be summarized as follows: Perregaard taught the end product of the instant case and the process of the instant case, and while not explicitly conducting the reaction of the instant case on 5-chloroindole it was clearly performed on very similar starting material (the 5-fluoroindole) and was explicitly singled out among the four methods as the "preferred" method. Subsequently, improvements to the conditions of the Ullmann arylation were developed (use of diamine ligands as taught by Klapars, and Kang), and the applicant has simply applied these new milder conditions to the old Perregaard materials. These facts can lead to only one conclusion, namely that the invention is obvious over the prior art.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-2 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims recite “an anion that does not react as a nucleophile and does not compete with the indole for the reaction with the 4-fluorophenylhalide, nor inactivates the copper catalyst”. What does this mean? The language renders the scope of this claim unclear. What anions are not nucleophiles? It is unclear the scope of the monopoly to be granted because defining a compound this way has no correlation with the chemical structure.

Claim Rejections – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

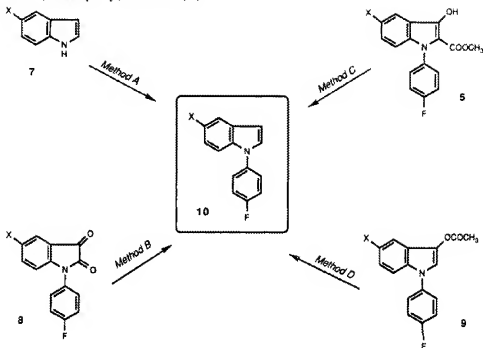
5. Claims 1-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Perregaard et. al. *Journal of Medicinal Chemistry* **1992**, 35, 1092-1101 (cited on the IDS) AND Klapars et. al. " *Journal of the American Chemical Society* **2001**, 123, 7727-7729 (cited on IDS) OR Kang S.K. et. al. *Synlett* **2002**, 3, 427-430 (cited on the IDS) in further view of Sarges et. al. *Journal of Medicinal Chemistry* **1989**, 32, 437-44. The claims are drawn towards a copper catalyzed arylation of a particular indole, namely 5-chlorindole which is converted to 5-chloro-1-(4-fluorophenyl)indole. This compound is an intermediate in the synthesis of sertindole. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

Determination of the scope and content of the prior art

(MPEP 2141.01)

Perregaard et. al. teach the synthesis of the compound of the instant case, 5-chloro-1-(4-fluorophenyl)indole, via four different methods. This is graphically represented in his scheme II, shown below:

Scheme II. Syntheses of 1-(4-Fluorophenyl)-1H-indoles (10)



Perregaard goes on to say that the copper catalyzed arylation is the preferred method of making these compounds (this is his method A):

“Literature procedures, albeit very rare, for the preparation of 1-phenylindoles either involve copper-catalyzed Ullmann arylation with aryl halides or nucleophilic aromatic substitution²³ of corresponding fluorobenzenes by 1-unsubstituted indoles. **The Ullmann arylation procedure (method A, Scheme 11) was preferred when 1-unsubstituted indoles (7) were either commercially available at reasonable costs and quantities or if they could be conveniently prepared according to known methods.** The 5-unsubstituted (10a), 5-NO₂ (10b), 5-CN (10c), and 5-F (10d) 1-(4-fluorophenyl)-1H-indoles are prepared accordingly (Table 11).…… The 5CF₃ (10f), 5-methylsulfonyl (10g), and 5-Chloro (10h) compounds were synthesized by method C (Table 11).

Table II. 1-(4-Fluorophenyl)-1*H*-indoles (10)

compd	X	method ^a	mp, °C	formula ^b
10a	H	A	40	C ₁₄ H ₁₀ FN
10b	NO ₂	A	144–145	C ₁₄ H ₉ FN ₃ O ₂
10c	CN	A	110–112	C ₁₅ H ₉ FN ₂
10d	F	A or B	oil ^c	
10e	CH ₃	B	oil ^c	
10f	CF ₃	C	53	C ₁₅ H ₉ F ₄ N
10g	CH ₃ SO ₂	C	126	C ₁₆ H ₁₂ FNO ₂ S
10h	Cl	C or D	86–87	C ₁₄ H ₉ ClFN
10i	OCH ₃	D	96	C ₁₅ H ₁₂ FNO
10j	Br	D	101	C ₁₄ H ₉ BrFN

^a See Scheme II and Experimental Section for reaction conditions. ^b Microanalyses (C, H, N) were within $\pm 0.4\%$ of the theoretical values. ^c ¹H NMR spectra are reported in the Experimental Section for compounds which were obtained as an oil.

Klapars who worked in the Buchwald group at MIT developed milder conditions for the arylation of indoles via the Cu salt catalyzed reaction, with various diamine ligands of the instant claims. The paper of Klapars summarizes it this way:

“While the importance of such reactions cannot be overstated, the necessity to use high temperatures, highly polar solvents, and often large amounts of copper reagents have prevented these reactions from being employed to their full potential. We have previously disclosed Ullmann-type methodology for the N-arylation of imidazoles¹¹ and for the formation of diaryl ethers.¹² Both of these used 1,10-phenanthroline/(CuOTf), benzene with various additives. This led us to examine the efficiency of other chelating nitrogen ligands in copper-catalyzed carbon-heteroatom bond forming processes. We show here that the combination of air stable CuI and racemic trans-1,2- cyclohexanediamine (1a) in the presence of K₃PO₄, K₂CO₃, Cs₂CO₃, or NaOt-Bu comprises an extremely efficient and general catalyst system for the N-amidation of aryl and heteroaryl iodides and bromides and the N-arylation of a number of heterocycles.” (conclusions)

Kang et. al. teaches the use of several other diamines in reactions of this type including EDTA.

Ascertainment of the difference between the prior art and the claims

(MPEP 2141.02)

The compound of the instant case (compound 10f of Perregaard et. al.) was prepared by method C or D, as per table II. Perregaard did not prepare the particular indole by his method A (the Ullman arylation that of the instant case). The instant process differs from that of Klapars or Kang, in that they don't prepare the particular indole recited here, although they teach exactly the same reaction conditions.

Finding of prima facie obviousness

Rational and Motivation

(MPEP 2142-2143)

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to use the process of Klapars (that of the Buchwald group) OR Kang to produce the instant invention. The experienced process chemist, would be motivated to use this method because it is the preferred method, gives higher yields under milder conditions, and leads to an important intermediate in the manufacture of a drug. Perregaard states that "The Ullmann arylation procedure (method A, Scheme 11) was preferred" and his work is very nearly anticipatory for some of the claims of the instant case. Far before this, Sarges et. al. suggested that the Ullmann arylation as a preferred method for the synthesis of 1-arylindoles:

"A more attractive and general route to 1-aryloxindoles, which avoided the formation of positional isomers, **involved the preparation of arylindoles B by a modified Ullmann reaction of indole with substituted aryl iodides or bromides in the presence of cuprous bromide and sodium carbonate in refluxing N-methyl-2-pyrrolidinone** and subsequent conversion with N-chlorosuccinimide and H_3PO_4 /acetic acid. 11" (pg. 438 column 2) Sarges et. al. *Journal of Medicinal Chemistry* **1989**, 32, 437-444.

In fact these workers simply rediscovered a very ancient reaction (perhaps uncredited, where the benzofused analog of indole was arylated) Dunlop, Helen G.; Tucker, S. Horwood. "Attempts to prepare optically active trivalent nitrogen compounds. I. Syntheses of 1,9-phenylenecarbazole and derivatives." *Journal of the Chemical Society* **1939**, 1945-1956.

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9-Phenylcarbazole.—A mixture of carbazole (5 g.), iodobenzene (12 g.), anhydrous potassium carbonate (5 g.), and copper bronze (0.3 g.) was heated at 190–200° for 6 hours. After cooling, the product was washed with warm water, and the residue crystallised three times from alcohol, forming colourless crystals (4.5 g.), m. p. 91–93° (yield, 65%) (Found: C, 88.7; H, 5.6; N, 5.66. Calc.: C, 88.9; H, 5.35; N, 5.8%). Cassella (D.R.-P. 224,951) gives m. p. 82–84°; Eckert, Seidel, and Endler (*J. pr. Chem.*, 1922, **104**, 87) give m. p. 87–89°; *Organic Syntheses*, 1928, **8**, 119, gives m. p. 88–89° and 88% yield. The *picrate* formed scarlet needles, m. p. 126–129° (Found: C, 60.9; H, 3.6; N, 11.8. $C_{15}H_{13}N \cdot C_6H_5O_7N_3$ requires C, 61.0; H, 3.4; N, 11.9%).

where the authors stated: "The effect of the addition of copper on the condensation of carbazole (+ potassium carbonate) with compounds of the formula 1-chloro-2-nitro-4-R-benzene remarkable.."

1948

Dunlop and Tucker: Attempts to prepare

R.	Temp.	Time (hrs.).	Yield (%).	
			Without Cu.	With Cu.
H	240–250°	3	10	50–60
Me	220–230	3	10	35
Cl	220–230	3	0	35
	230–240	7	10	—
NO ₂	170–180	12	50	50
CN	180–190	12	40	15

Similarly for carbazole (+ potassium carbonate) and the following three substances:

<i>p</i> -Iodotoluene	180–200	6	40	66
<i>p</i> -Chloroiodobenzene	200	6	17	76
Ethyl <i>p</i> -iodobenzoate	220–230	6	0	80

In addition, Klapars suggests that this is an important route (especially since the instant case substrate, 5-chlorindole, has the electronic characteristics described):

"The nucleophilic aromatic substitution of aryl halides, activated by electron-withdrawing substituents, with indole represent an alternate route to N-arylindoles for some substrate combinations." Klapars et al. *ibid*.

The applicant is using the process, just as Perregaard recommends to make an important drug intermediate. A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976). In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as

a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

One of ordinary skill is also one of “ordinary creativity, not an automaton”. See *Leapfrog Enterprises Inc. v. Fisher-Price. and Mattel Inc.* UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT “An obviousness determination is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. See *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. , 2007 U.S. LEXIS 4745, 2007 WL 1237837, at 12 (2007) (“The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.”).

The opinion set forth in *In re Larsen* (CCPA 1961) 292 F2d 531, 130 USPQ 209 is relevant:

A case in point is *Wirebounds Patents Co. et al. v. H.R. Gibbons Box Co.*, 25 F.2d 363 (CCA 7th Circuit). In holding the method claims there involved unpatentable, the court said: Moreover, the method patent contains nothing but the natural and obvious method of producing the box. It cannot be considered invention to describe and claim a process, or to produce a machine, or formulate a method which any successful mechanic would produce when required to effectuate a given result. The process claims define, in effect, only the reaction of A with B to produce AB, the reaction admittedly being old except for the selection of A and B from the mass of known materials available. Though they point out novel subject matter, these claims, tested against the prior art, do not define anything unobvious to one of ordinary skill in this art.

This art is chemistry. Were we in a mechanical art, **I think no one would trouble to argue that every time a new tool or machine is invented one can obtain process claims directed to nothing more than the obvious steps of selecting the materials, forming the parts on suitable machines, and assembling them in their operative relationship. I can see no distinction in principle here.** Yet that is what applicant contends in advancing in his conclusion. (emphasis added)

As pointed out in *In re O’Farrell*, 7 USPQ2d 1673 (Fed. Cir. 1988) “For obviousness under §103, all that is required is a reasonable expectation of success.”

It is therefore submitted that the claims are properly rejected as unpatentable over what is already known in the art, and that they recite no more than the obvious application of an old reaction.

Conclusion

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David K. O'Dell whose telephone number is (571)272-9071. The examiner can normally be reached on Mon-Fri 7:30 A.M.-5:00 P.M EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on (571)272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

D.K.O.

/Rita J. Desai/
Primary Examiner, Art Unit 1625

